

1 device-related complications, including loss of  
2 function, extensive wear, the Harris Hip Score, and  
3 revision surgeries.

4 Success is measured at one year based upon  
5 patient success, in which there are no device-related  
6 complications. The Harris Hip Score is greater than  
7 or equal to 80. And revision surgeries are also  
8 absent. Study success requires that at least 95  
9 percent of the patients in that study at one year are  
10 deemed successful.

11 Let's go back and review what the FDA says  
12 about least burdensome because I think this is a key  
13 element in making our recommendations to the FDA. And  
14 that is least burdensome guidelines are a successful  
15 means of addressing pre-market issues that involve the  
16 most appropriate investment of time, effort, and  
17 resources on the part of industry and the FDA.

18 With that, I would like to set the stage  
19 for where total hip replacement has been and where it  
20 is today. There is no question that total hip  
21 arthroplasty is one of the most successful operations  
22 ever invented, thanks in part to this gentleman and

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1 also thanks in part to the documentation provided by  
2 Dr. Callaghan, who published these results just  
3 recently in *Journal of Bone and Joint*. This includes  
4 30-year follow-up of Dick Johnston's series with  
5 excellent results going as far out as 31 years or so.  
6 These were all with small, 22-millimeter head  
7 stainless steel Charnley stems, finger-packed cement,  
8 a transtrochanteric approach. And, yet, at 30 years,  
9 we still see an acceptable result.

10 On the left is this woman at 58 years at  
11 the time of her implantation. And here she is at 31  
12 years later, age 89, still living on her Iowa farm.

13 However, to get to that point, success did  
14 not come easily. This is one of the earlier Charnley  
15 hips, stainless steel head but articulating against a  
16 Teflon cup. This wore out within the first two years  
17 of function.

18 Also available to the panel and for  
19 general discussion is the NIH consensus statement,  
20 which was written ten years ago. Even at that time,  
21 they stated, "As of 1994, the state of the art  
22 pertaining to total hip replacement has changed

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1 substantially compared to the NIH consensus statement  
2 on total hips from 1982. At that time, they mentioned  
3 problems with osteolysis, particulate debris, and  
4 fixation."

5 They noted that success was supported by  
6 30 years of follow-up data. They also noted that  
7 various total hip design, fixation methods, and  
8 surgical technique need to be rigorously compared with  
9 one another and that it also depends upon surgeon  
10 experience and the hospital environment.

11 Additional areas of evaluation that they  
12 suggest should include rehabilitation interventions  
13 and patient-level predictors, patient expectations,  
14 demographic characteristics, comorbidities, obesity,  
15 and activity level, as you have heard before.

16 They also summed this up, saying  
17 "Long-term follow-up is essential to determining  
18 outcomes and pathological processes. Failures related  
19 to osteolysis and particular debris were identified  
20 only by long-term follow-up of patients."

21 That was 1994. What's the nature of total  
22 hip arthroplasty today? First of all, we have

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1 multiple combinations of components available to us  
2 today; in part, because surgeons and manufacturers  
3 sought to eliminate the problem of both osteolysis and  
4 the problems with fixation.

5 We had metal and metal articulation, which  
6 brings up the problem of metal ion concentrations in  
7 the blood, as pointed out by Sabarino, *Journal of*  
8 *Biomedical Materials Research*, 2002. Subset A is the  
9 metal on metal group, showing about twice the amount  
10 of cobalt in the blood as the metal on plastic group.  
11 They also detected a significant difference in the  
12 level of chromium ion concentration.

13 What is not apparent is what is the  
14 significance of those numbers and what are the  
15 long-term effects of having those levels of ions in  
16 one's blood.

17 Also, total hip arthroplasty is evolved  
18 into a family of procedures: the small incision  
19 posterior approach; the small incision anterior  
20 approach; the two incision fluoroscopic; the small  
21 incision Kegy; and if you have been sleeping somewhere  
22 else for the last five or six years, the good old

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1 standard posterior approach and anterior and  
2 anterolateral. There are entire catalogs devoted to  
3 the new instrumentation utilized in these approaches.

4 In addition to new instrumentation and new  
5 implants, we have new approaches to the implantation  
6 of these devices, including computer navigation  
7 systems, which are quickly coming on the market.

8 It is no secret that many orthopedic  
9 surgeons are out there advertising their ability to do  
10 these procedures, promising less anesthesia, less  
11 blood loss, less pain, fewer complications, shorter  
12 stay, shorter recovery. And I'm sure they anticipated  
13 some type of FDA involvement because they include this  
14 disclaimer, "Do not attempt to treat yourself, your  
15 child, or anyone else without proper medical  
16 supervision." I'm not making this up.

17 As you have seen before, there are  
18 national joint registries available around the world,  
19 including the Swedish Total Hip Replacement Register  
20 recently reported on.

21 These are some of their results. I won't  
22 go into them in detail other than to mention that at

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1 seven years, most of those survival rates are 95  
2 percent and above except for two devices, which were  
3 readily taken off the market. And their failure rate  
4 is readily evident in that column.

5 So the panel is asked to address these  
6 questions: study duration, patient selection, outcome  
7 measures, post-market studies, and hip systems.

8 As has been stated before, 24 months of  
9 evaluation has been the accepted study length in the  
10 past. This is an empirical time point. And it's a  
11 requirement if you plan to get your study published in  
12 the *Journal of Bone and Joint Surgery*. Data points  
13 are taken at baseline, 6 weeks, 6 months, 12 months,  
14 and 24 months.

15 Data points at six weeks and six months  
16 are useful in detecting early complications related to  
17 both technique and perioperative protocols. Data  
18 points at 12 and 24 months can detect failures of  
19 materials and device incorporation. And it requires  
20 more than 24-month follow-up to look at long-term  
21 effects. That long-term follow-up may be years,  
22 decades even.

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1 Patient selection. The indications for  
2 total hip replacement is extending to both younger and  
3 to older patients. The younger patients tend to have  
4 a more active lifestyle, and the older patients tend  
5 to have more comorbidities. Historically, the rate of  
6 total hip arthroplasty has been associated with race  
7 and with level of income, even though the incidence of  
8 disease is similar in most places and across  
9 socioeconomic boundaries.

10 In the initial study of a device, one  
11 might consider stratification of patients because we  
12 have such a wide selection of patients available to  
13 us. Earlier studies were more uniform because those  
14 studies were aimed particularly at older individuals  
15 within a certain age range. Now we can go anywhere  
16 from 18 to 90 years of age.

17 As has been pointed out, data can be more  
18 powerful with grouping, especially if there are no  
19 concurrent randomized controls. However, the number  
20 of the patients may vary depending upon the variables  
21 being studied.

22 The Harris Hip Score has been validated

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1       against other available outcomes measures. It is  
2       familiar to all orthopedic surgeons. It is readily  
3       available to investigators. And it is free. It  
4       provides cross-study comparisons. And, as a point of  
5       reference, a Harris Hip Score of over 90 is considered  
6       excellent.

7               However, it may be important to also  
8       consider the effectiveness of total hip arthroplasty  
9       and not just its survival. To do that, we need to  
10      look at additional outcome measures, such as quality  
11      of life survey and disease-specific surveys.

12             Those additional outcome measures can  
13      include the SF-36, now in version 2, health survey of  
14      the quality of life. It is widely accepted and  
15      rigorously validated. It has been translated into  
16      over 50 languages. And now online scoring is  
17      available at 50 cents per record.

18             We also had the WOMAC osteoarthritis  
19      index, which is currently available in 65 languages.  
20      Should we be using these outcome measures in all of  
21      our total hip studies? Well, we have to look at it in  
22      two frameworks.

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1           One is to look at total hip replacements  
2           as a device. The Harris Hip Score has a documented  
3           successful history and correlates well with certain  
4           aspects of these more detailed scoring systems,  
5           particularly in the physical realm.

6           If we look at total hip replacements as a  
7           way of life, my editorial opinion would be that would  
8           be nice, but it requires much more detailed  
9           instruments; added expense and time, as has been  
10          pointed out earlier; and those results are affected by  
11          factors that are beyond the scope of the implant  
12          itself.

13          What about the endpoint of Harris Hip  
14          Score greater than 80 at one year? Well, what Harris  
15          Hip Score would I like to see? I like to see a  
16          greater than 90 in every case because everybody wants  
17          to score a touchdown, but Harris Hip Score is  
18          acceptable to me without getting upset. Eighty or  
19          better is not bad. So we are settling for a five-yard  
20          gain.

21          I think the sponsors have been very  
22          conservative in setting 80 as a cutoff because just a

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1        few problems with the Harris Hip Score would then  
2        lower their success rate. So they are being very  
3        generous to the FDA in setting the level at that  
4        level.

5                    What time interval is appropriate for  
6        cutoff? Early failures may not be evident at 12  
7        months, particularly in older patients, who may still  
8        be recovering strength. Early evaluation at six weeks  
9        and six months is still useful for the reasons I have  
10       mentioned before. However, apart from gross failure,  
11       there may be a tendency amongst orthopedic surgeons to  
12       give time a chance at a one-year time frame, as  
13       opposed to a two-year time frame. Again, this is only  
14       my persona opinion.

15                   Post-market studies. I believe those were  
16       available. I think continued follow-up is the norm  
17       for most total joint surgeons. Even with busy  
18       practices, we still follow our patients up at at least  
19       one, two, or three-year intervals. Routine  
20       radiographs are obtained on a regular basis. And we  
21       perform routine exams.

22                   As has been pointed out, we live in a very

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1 mobile society. And it is difficult to corral these  
2 patients back into the office on a regular basis. And  
3 in many cases, certain insurance companies will not  
4 reimburse the surgeon for that visit, placing another  
5 burden on the clinician.

6 However, it is important to communicate  
7 any overt failure of a total hip. As we have seen  
8 before in all of the data presented so far, this is a  
9 rare event in most series unless there is some grossly  
10 deficient material defect or manufacturing defect.  
11 Continued reporting on these gross failures should not  
12 be burdensome and can be accomplished with the patient  
13 ID card.

14 I will note that the U.S. Total Joint  
15 Registry is still under development. It is not  
16 available yet, but it may be available in the future.  
17 Having said that, the cost of maintaining an  
18 individual institutional database is significant. The  
19 cost at Mayo Clinic is anywhere from 40 to 400  
20 thousand dollars, and I can't remember how many zeros.  
21 But there is data available.

22 In addition, surgeons continue to publish.

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1 And in order to publish in certain journals, they  
2 continue to collect data well past the two-year  
3 follow-up time frame.

4 With regards to hip systems, we have to  
5 remember these are modular devices. They have  
6 interchangeable bearing surfaces. They have  
7 interchangeable bearing geometry. Also, by its very  
8 nature, the total hip has independent acetabular and  
9 femoral implants, and it is not always required to  
10 have the devices coming from the same manufacturer.

11 There is a tendency by some surgeons to  
12 mix and match fixation and also to mix and match  
13 materials as well. My only comment on this is that if  
14 this is part of an ongoing study for FDA approval,  
15 that it is important for one to stick to the script,  
16 at least for that cohort.

17 I would like to thank the panel for this  
18 opportunity to present. And I welcome the comments of  
19 the sponsors. Thank you.

20 CHAIRPERSON YASZEMSKI: Thanks very much,  
21 Dr. Mabrey.

22 Dr. Larntz, can we ask for your

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1 presentation?

2 MEMBER LARNTZ: Thank you.

3 A few comments. Ms. Silverman did an  
4 excellent job, by the way, giving you your statistics  
5 lesson for the day. This is an area where statistics  
6 lessons are needed because people get very easily  
7 confused. The way I think of these OPCs -- can I use  
8 OPC? Does everyone understand? Objective performance  
9 criteria.

10 This is a guidance document that was  
11 submitted, but the key element of this guidance  
12 document is that it proposes to say the right kind of  
13 study is a one-arm study with some objective  
14 performance criteria to say this is an okay device.  
15 To me, that is what is there.

16 The guidance document, you can have a  
17 guidance document on a randomized trial. That is  
18 perfectly okay, you know. And there are such.

19 There are guidance documents set up with  
20 OPCs in them. And I think it is instructive to go  
21 look at those. After all, I mean, what else do I do  
22 with my new computer since my last one burned out? So

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1 I downloaded those and looked at them.

2 There is one for some ophthalmic  
3 intraocular lens, whatever. And that was interesting.  
4 It is about 66 pages. It says studies should have at  
5 least 300 patients. And, actually, there are OPCs in  
6 there. Actually, I didn't read it thoroughly enough.  
7 They gave what they call a grid, FDA grid of outcomes.

8 So what they have is many, many -- hard to  
9 remember now. It's been a few days, like three or  
10 four, but they gave a list of many, many outcomes and  
11 then a whole series of studies that show you what the  
12 outcomes were for those, what came out of those.

13 And what a sponsor should do is do at  
14 least 300 patients and then report data for these  
15 outcomes. And then you can compare. That is one way  
16 to do it.

17 The cardiac ablation catheter guidance  
18 document is a dream. Dr. Yaszemski would love it. It  
19 is eight pages long. Okay? It is short, to the  
20 point. I'm sorry? Did I say something wrong?

21 CHAIRPERSON YASZEMSKI: No, sir.

22 MEMBER LARNTZ: Direct. It says that,

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1 really, what we want for cardiac ablation catheter is  
2 we have three endpoints, separate endpoints. By the  
3 way, the intraocular lens also treated the endpoints  
4 distinctly. Each endpoint was treated distinctly. Do  
5 you hear what I am saying?

6 From what we have here, we have something  
7 very different here because someone is proposing a  
8 composite endpoint. I will say what I think about  
9 that in a second, although you might have an opinion  
10 already from the way I am going. Okay?

11 Three separate endpoints: an acute  
12 success, whatever that means, nice name; chronic  
13 success; -- that's also a nice name -- and major  
14 complications, three separate endpoints. And they set  
15 up target values. It's very nice, 95 percent for  
16 acute success, chronic success at 90 percent, major  
17 comps, two and a half percent. And it's actually  
18 better than each of those. That's the target.

19 And then they actually tell you you should  
20 use one-sided confidence intervals, which I think is  
21 actually okay here because what you are really trying  
22 to do here is say, is this device good enough? So do

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1       you know enough to set up standards? I'll call them  
2       target values, standards.

3               And then you have to decide how close do  
4       you have to be to that standard to say this device is  
5       good enough? In the typical randomized trial, we are  
6       trying to say, is this device close enough to another  
7       device? Here we are trying to say, is this device  
8       good enough compared to all of history of devices? It  
9       sounds like there is credible data here on hip  
10      replacement surgeries. Yes, incredible amounts of  
11      data.

12              I am of the opinion that we probably might  
13      be better off -- and this is where my other  
14      statistical colleagues may get mad at me. We may be  
15      better off using these historical data to do our  
16      comparisons if we can do the right matching because  
17      there is so much of it.

18              In randomized trials, things can go wrong.  
19      I know a doctor -- I'd better not say his name because  
20      he lives within this area -- who did a study. And it  
21      was a cardiovascular study. So it's not orthopedic.  
22      But I know a doctor. And he did a randomized trial.

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1 It was a very small study, about 30 or 40 patients in  
2 each arm. But all of the patients in the control  
3 group did awful, awful. You would be embarrassed if  
4 they were your patients.

5 But guess what. The ones in the treatment  
6 group did okay, not great, just okay. That meant it  
7 was highly statistically significant and because he  
8 had an awful control group, which when he's questioned  
9 under extreme conditions, he says, "Well, it must have  
10 been chance. I couldn't have been that bad."

11 Well, except that he was really smart. He  
12 said, "I'm going to use that control group again. He  
13 put another up study up and then used this old control  
14 group that was really lousy.

15 So control groups can go wrong. I don't  
16 disagree with that. So if you've got so much data and  
17 you can do the matching or if you can really decide  
18 what is good enough, then I think it is okay.

19 The other area that they are used in is in  
20 heart valves. This one you wouldn't like. It is five  
21 .pdf files, at least 100 pages, very detailed. What  
22 they do is they look at adverse events in this

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1 objective performance criteria. And they actually  
2 have listed seven different adverse event objective  
3 performance criteria, seven different ones. And they  
4 have a general policy there.

5 You have got these target values. And  
6 what you have to prove is that you do no worse than  
7 doubling those target values. You have to prove you  
8 are statistically better than that. Again, on one  
9 side, the confidence interval is what is used there.

10 Now, what am I saying here? You have some  
11 experience. Thank you, Dr. Buch, for at least  
12 pointing these out in your document and your review  
13 that we can use. All of them use multiple outcomes  
14 and set up criteria with multiple outcomes. I think  
15 that is the way we should go about it here.

16 I am not of the opinion that the composite  
17 outcome is the kind of thing because, just a second  
18 now, what if you had a Harris Hip Score, everyone  
19 passed it? We said everyone passes, right? Everyone  
20 passes. But five percent of your patients had  
21 revisions at one year. How would you feel about that  
22 hip replacement device? Would you feel like 95

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1       percent is your target, 95 percent with 5 percent  
2       replacements? How would you feel about that? Well,  
3       you would have to decide, wouldn't you?

4               If I look at this historical data, that  
5       wouldn't be so good, right, five percent failure at  
6       one year? And you have to imagine if you are using  
7       the composite score, you have to imagine that if you  
8       really believe in the composite, you don't get a  
9       chance to guess later, "Oh, I really think was more  
10      important. That was more important."

11             I believe you should set standards for  
12      each one of these separately. Okay? Standards for  
13      each one of these separately, not use the composite.  
14      There should be a standard, a low rate presumably, for  
15      revisions.

16             I think most revisions might be involved  
17      with a complication. So you might get a little higher  
18      rate for complications and a Harris Hip Score of  
19      whatever you want.

20             So I think you should use that, I think  
21      then obviously the confidence interval approach or  
22      test. I think the confidence interval approach is

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1 just fine. To say that you are good enough or within  
2 a detail, the non-inferiority margin in the target is  
3 the way to go. I think that is what I would like to  
4 do.

5 So I guess the summary is we have to  
6 decide -- or not you. We have to give advice. We  
7 don't decide anything. That is what we keep being  
8 reminded of as the panel. We give advice, but is  
9 there enough data out there? Then when you form the  
10 objective performance criteria, I don't believe in  
11 picking one out of the air.

12 Where did 95 percent come from? Well, I  
13 didn't see a large meta analysis supporting 95  
14 percent. I think it takes a lot of work. I know Dr.  
15 Grunkemeier, who did the work for the heart valve  
16 guidance document, did a tremendous amount of work to  
17 decide what the objective performance criteria need to  
18 be. That's a very key feature of what the criteria  
19 should be. It should be for multiple endpoints.

20 And then there is statistical methodology  
21 that will help you. Once you decide what the  
22 non-inferiority margin is, statistical methodology can

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1 help you decide on a sample size and so on.

2 Thank you.

3 CHAIRPERSON YASZEMSKI: Thanks, Dr.  
4 Larntz.

5 What we have remaining to do is a general  
6 discussion based on all of these presentations and the  
7 six questions and then specific attention to each of  
8 the six questions.

9 What I would like to suggest we do now is  
10 take just five minutes to stretch and use the  
11 restrooms, then come back and get started. It's 2:47.  
12 Let's come back about 2:52 or so.

13 (Whereupon, the foregoing matter went off  
14 the record at 2:48 p.m. and went back on  
15 the record at 2:53 p.m.)

16 CHAIRPERSON YASZEMSKI: The first part of  
17 the discussion will be general and be an opportunity  
18 for panel members to bring up any issues they have  
19 heard or have questions about from either the  
20 petitioners' speeches, the FDA's speeches, or our lead  
21 reviewers' speeches.

22 I might ask first, does anybody have

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1 anything they say to open? Dr. Naidu?

2 MEMBER NAIDU: I just have a question for  
3 clarification. Are we talking about all hip systems,  
4 like metal on metal, or are we just talking about  
5 metal on polyethylene?

6 CHAIRPERSON YASZEMSKI: I will have to ask  
7 for clarification from Dr. Witten.

8 DR. WITTEN: Yes. I think the guidance is  
9 for all hip systems. That is actually one of the  
10 questions that Dr. Buch has at the end, which is if  
11 there is any that you think need some other special  
12 attention for some reason. I also want to mention  
13 that the most familiar kinds of hip joints wouldn't  
14 require clinical studies.

15 So, in other words, it wouldn't be that  
16 useful if it's just applied to your typical total hip  
17 that didn't have any features that would require  
18 clinical studies, like most metal poly hips.

19 CHAIRPERSON YASZEMSKI: Mr. Batts, do you  
20 have a comment on that? Other comments of a general  
21 nature? Dr. Mabrey?

22 MEMBER MABREY: Yes. A question for Dr.

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1       Stulberg.   Dr. Stulberg, where do you see these  
2       guidelines fitting into the overall I guess  
3       investigative milieu of joint replacement these days?  
4       How does it fit in with ongoing research studies,  
5       publications, and the like?

6                 DR. STULBERG: I think one of the things  
7       that drove this particular process is we see device  
8       evaluations occurring outside of the United States  
9       environment.

10                I think the academic communities are  
11       suffering from the burden of studies that sometimes  
12       seem more involved than they might need to be given  
13       the 30-year track record of joint replacement at the  
14       hip, which has been very predictable.

15                I think this type of approach may be very  
16       useful for evolution in devices. A lot of device  
17       changes occur as small, little steps that improve  
18       first fixation or then strength of devices. There are  
19       lots of steps like that, and it has become a very  
20       predictable operation.

21                This kind of approach might allow a  
22       manufacturer and an investigator to look at these

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1 types of new but not particularly way out there  
2 devices for hip replacement in a predictable way and  
3 get them into the marketplace faster, where they can  
4 help patients and hopefully improve the durability of  
5 a product. So that's I think how many of the  
6 clinicians involved in this felt this might be useful.

7 CHAIRPERSON YASZEMSKI: Thanks, Dr.  
8 Stulberg.

9 Other comments? Dr. Finnegan?

10 MEMBER FINNEGAN: I actually have a  
11 question for Dr. Larntz, but I am probably going to  
12 make a fool of myself. I had recently to do some  
13 writing. And I looked up an article by Somer and  
14 Zigger. They talk about using a subset control; in  
15 other words, a much smaller control group, and that  
16 that will work as well to give you your results.

17 Does that make any sense at all? And if  
18 so, is that a possibility given the historical  
19 background of this implant?

20 MEMBER LARNTZ: I am not familiar with  
21 their work.

22 MEMBER FINNEGAN: They were talking about

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1 intent to treat is basically looking at how good your  
2 research protocol is; whereas, biological efficacy  
3 needs to evaluate what actually happens and that when  
4 you look patients from your population groups, you  
5 usually lose more from the control group than you do  
6 from the study group because the study group is  
7 interested in how things are going. So they took a  
8 subset of their control group.

9 Does that make any sense?

10 MEMBER LARNTZ: Yes. I mean, I can  
11 understand how they are doing some matching there to  
12 make sure. What they are talking about is matching to  
13 eliminate the bias from the dropouts.

14 MEMBER FINNEGAN: Right.

15 MEMBER LARNTZ: And that is possible to  
16 do.

17 MEMBER FINNEGAN: I guess my question is,  
18 there is some concern here about cost and time and  
19 everything else. Could we design a smaller control  
20 group given the historical background?

21 MEMBER LARNTZ: Honestly, to tell you the  
22 truth, I am very leery of small control groups because

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1 of the story I just told, that, in fact, all you need  
2 is your control group to do badly and you win.

3 CHAIRPERSON YASZEMSKI: Thanks, Dr.  
4 Larntz.

5 Other comments of a general nature?

6 (No response.)

7 CHAIRPERSON YASZEMSKI: If not, we are  
8 going to move to question one and probably get a more  
9 detailed discussion as we go through the six  
10 questions. Let's move to question one Dr. Buch has  
11 put up. Question one asks us about the adequacy of  
12 the composite endpoint criteria and each individual  
13 component at the defined time point, the necessity of  
14 other endpoints, and the adequacy of sample size,  
15 delta, confidence intervals.

16 Would anybody like to start off with  
17 comments or questions of any of the presenters on the  
18 issues of question one? Dr. Mabrey?

19 MEMBER MABREY: A question again for the  
20 sponsors. I had a chance to talk to Dr. Stulberg just  
21 a moment ago, but I would like to get a feel for how  
22 hard and fast the sponsors are focusing on this

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1 one-year endpoint and what your thoughts are and why  
2 that would be better than, let's say, 24 months.

3 CHAIRPERSON YASZEMSKI: I might add I will  
4 ask Dr. Stulberg to say now that is question two. We  
5 can mix and match them.

6 MEMBER MABREY: Oh, sorry.

7 CHAIRPERSON YASZEMSKI: That is okay. We  
8 will get to that, though, if that is okay, in question  
9 two.

10 Dr. Witten?

11 DR. WITTEN: Yes. I will say, though,  
12 that I think it is appropriate to at least mention it  
13 because some of these issues, like what is your  
14 target, --

15 CHAIRPERSON YASZEMSKI: Right.

16 DR. WITTEN: -- is really also related to  
17 what the duration is you have in mind.

18 CHAIRPERSON YASZEMSKI: Right. And I  
19 think since FDA wants to hear what we think about all  
20 of these, it is okay. We don't have to consider them  
21 separately, as we did in the reclassification.

22 Dr. Stulberg, can we ask you to comment on

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1 these, please?

2 DR. STULBERG: Certainly. The general  
3 sense of where new hip replacement systems develop --  
4 and if you look at the long-term data, we don't see  
5 our problems very easily before five to ten years.  
6 What we want to see are the significant problems that  
7 are going to occur within the first 12 to 24 months  
8 after device.

9 The clinical community was divided,  
10 probably a little more comfortable with 24 months than  
11 12. But the sense of the data is that if you are  
12 looking for catastrophic failure in devices, you are  
13 likely to find it within the first 6 to 12 months. So  
14 there were people who were not uncomfortable with the  
15 12-month number, but I think you could let that  
16 statistically play out and see.

17 If you found that you really didn't need  
18 24 months, why not let it go sooner? It is really  
19 down the road where you have trouble doing it. And  
20 that is a population very difficult to figure out at  
21 10 years and 15 and track.

22 CHAIRPERSON YASZEMSKI: Thanks, Dr.

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1 Stulberg.

2 Dr. Jacobs, would you like to comment on  
3 that?

4 DR. JACOBS: Thank you.

5 And I would draw your attention to some of  
6 Dr. Buch's slides, where she was looking at the  
7 survivorship curves from the Scandinavian registries.  
8 You will not see a difference between one and two  
9 years.

10 My sense is there is probably a lot of  
11 information, particularly manufacturers have,  
12 comparing one and two-year outcomes. One possibility  
13 is that a more firm rationale could be provided by  
14 essentially mining that data to show potential or no  
15 differences between the one and two-year outcome  
16 points.

17 I agree with Dr. Stulberg. When we see  
18 failures, catastrophic failures, -- and I can think of  
19 the two most recent problems that I can think of -- we  
20 were well-aware of them before 12 months. It's very  
21 unlikely -- and I cannot think of an instance where we  
22 found a problem between 12 and 24 months.

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1 CHAIRPERSON YASZEMSKI: May I ask Dr.  
2 Jacobs? Dr. Larntz had talked about separating  
3 endpoints into acute success and major adverse events.  
4 It sounds like those things can be addressed in a  
5 short period of time; i.e., one year, and that they  
6 are unlikely, as you just suggested, to show up  
7 between years one and two.

8 But then he said separating the chronic  
9 success, the long-term endpoint. I wonder if you  
10 might comment on how to do that because if the  
11 problems exist currently at 10 to 15 and perhaps 20  
12 years out, we are never going to get them in the  
13 pre-market studies.

14 How should we address them? Is this where  
15 the national registry is going to come in? Just your  
16 thoughts on that.

17 DR. JACOBS: I think this is where the  
18 national registry is going to come in. I think it is  
19 not practical to have a regulatory environment where  
20 you require large amounts of extremely long-term data.  
21 I just don't see that practical. I see it being  
22 problematic in terms of getting devices to the market

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1 in a timely fashion.

2 The registry is an effort that Dr. Mabrey  
3 mentioned. The academy is working very hard to get it  
4 going in the U.S. I remind everybody that there are  
5 successful registries in Finland, Norway, Sweden, in  
6 Australia, U.K., and others. So I hope we can move  
7 forward with this effort and get the appropriate  
8 governmental support that we need.

9 CHAIRPERSON YASZEMSKI: Right. Thanks,  
10 Dr. Jacobs.

11 Other thoughts about question one?

12 DR. BUCH: Can I make a comment?

13 CHAIRPERSON YASZEMSKI: Yes, Dr. Buch?

14 DR. BUCH: I hate to be a fly in the  
15 ointment, but there are actually things that are not  
16 published in the historical literature that show that  
17 there are device complications between one and two  
18 years.

19 And the one thing that pops into my mind  
20 as a recent occurrence are the fracture of the ceramic  
21 heads, femoral heads. That was not discovered in the  
22 first year, but it occurred in the 18 to 2-year period

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1 post-op.

2 CHAIRPERSON YASZEMSKI: Thanks, Dr. Buch.

3 Other comments? Mr. Craig?

4 MR. CRAIG: Yes, just a couple of quick  
5 comments. As far as the one or two-year follow-up,  
6 anecdotally, yes, it is correct that we don't see a  
7 lot of difference between one and two-year.

8 As far as the long-term, picking up  
9 long-term problems, we do have the MDR reporting as a  
10 requirement. It may be significant what years that  
11 occurs after a device is on the market. If we picked  
12 it up there, that would take it off the market if it  
13 came up.

14 In fact, that is the way the ceramic head  
15 came up. It was brought up in the MDR requirements.  
16 We saw that. It was not a clinical type study that  
17 picked it up. It was on the market at the time with  
18 a manufacturing problem. We picked that up and  
19 brought it off the market very quickly.

20 CHAIRPERSON YASZEMSKI: Right. Thank you,  
21 Mr. Craig.

22 Would anyone on the panel like to ask

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1 questions or make comments about the sample size, the  
2 delta, the confidence intervals? Dr. Larntz gave a  
3 very thorough discussion, but are there any other  
4 issues or questions to add to what he has already  
5 said? Ms. Maher, let's hear the industry rep's  
6 perspective on this?

7 MEMBER MAHER: Well, I think from the  
8 industry rep's perspective, from the industry  
9 perspective, we can take into account Dr. Larntz's  
10 comments. I wasn't detailed involved in setting up  
11 this guidance document, but it can be looked at in  
12 determining what is the better way to go in  
13 conjunction with the agency as we are going forward.

14 I would also, though, like to follow up  
15 since you have called on me on what Mr. Craig said on  
16 the MDR reporting. I know people around here have  
17 frequently whenever I brought up MDR reporting as a  
18 way to find problems or issues poo-pooed it and said,  
19 "Well, not everything is reported."

20 Well, I would, first of all, submit that  
21 if not everything is reported, that really is not the  
22 manufacturer's fault. It's the fault of the

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1 practitioners who aren't calling in that something has  
2 happened that may be device-related and that,  
3 actually, in many instances in my experience in the 12  
4 years I have worked in industry, the MDR process has  
5 found problems that we have solved. Most of them are  
6 not major recall-type issues, but things where  
7 continuous improvement comes into play. And that is  
8 where the general concept of design control as well  
9 comes into play to continually improve our products.

10 CHAIRPERSON YASZEMSKI: Thanks, Ms. Maher.

11 Dr. Witten, may I ask, with respect to MDR  
12 reporting, is this limited to clinicians or may  
13 patients call in an MDR report?

14 DR. WITTEN: They can call.

15 CHAIRPERSON YASZEMSKI: Because I wonder  
16 if a way to increase the MDR reporting, then, is since  
17 we have talked about this identification card to give  
18 patients include a little statement about the MDR and  
19 the phone number on their card.

20 MEMBER MAHER: Just to follow up on that,  
21 the MDR reporting, we as a company are responsible for  
22 reporting them to the FDA. And we report whenever we

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1 find anything.

2 So we report if we get it because of  
3 litigation. Even if we don't believe our device was  
4 at fault, those get reported. We report it when we  
5 hear it from the practitioners. We report it if we  
6 hear it from the customers. And a surprising number  
7 of patients do call the 800 number or they figure out  
8 the name of the CEO of the company and call him.

9 CHAIRPERSON YASZEMSKI: Good. Thank you.

10 Dr. Doyle, may we ask for your comments on  
11 this issue?

12 MEMBER DOYLE: I really don't have a lot  
13 to say.

14 CHAIRPERSON YASZEMSKI: Okay. That's  
15 okay. We want to be certain that you do if you have  
16 something to say.

17 MEMBER DOYLE: I am listening to whatever  
18 is being said more than making a comment.

19 CHAIRPERSON YASZEMSKI: Thank you.

20 Dr. Witten, have we discussed question  
21 number one adequately?

22 DR. WITTEN: No.

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1 CHAIRPERSON YASZEMSKI: What would you  
2 like to hear specifically from us?

3 DR. WITTEN: Yes. Thank you for asking  
4 me.

5 This really is the most critical question  
6 for us, I think. So I would like to spend a little  
7 bit more time on it if it's possible. I am going to  
8 maybe break this question down into what would really  
9 help us. Then if we can get a comment from the  
10 clinicians, that would be great.

11 So taking Dr. Larntz's suggestion of,  
12 instead of looking at a composite endpoint, looking at  
13 each of the three components of the endpoint, which --

14 MEMBER LARNTZ: Or more than three if  
15 there are other endpoints.

16 DR. WITTEN: Okay. Well, I want to focus  
17 on the things that really are the most critical, which  
18 are the device-related complications and, in  
19 particular, I should say, also the HHS score at 12  
20 months greater than or equal to 80 and the revision  
21 surgeries. This is page 3 of 44 of the guidance  
22 document that was provided to us by OSMA.

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1           For each of those, say patient success is  
2       defined the way that it is in this guidance document.  
3       Here is what we would like to know. What would be the  
4       lower bound of the 95 percent confidence interval that  
5       you would think acceptable to be demonstrated in the  
6       study?

7           So for each of those three, that is what  
8       we would like, a suggestion about the lower bound of  
9       the 95 percent confidence interval acceptable for each  
10      of those three parameters.

11           CHAIRPERSON YASZEMSKI: And those three  
12      again are device-related complications, the HHS score,  
13      and the number of revision surgeries?

14           DR. WITTEN: Right. And you might want to  
15      take them in reverse order because I think it will be  
16      more easy to answer C and then B. C and B will be  
17      easier to answer than A.

18           CHAIRPERSON YASZEMSKI: Let's start with  
19      revision surgeries if that is okay. Let's start. Dr.  
20      Mabrey, let's start with you and come around the horn.  
21      What do you think? Revision surgeries. What should  
22      be the lower bound for success at whatever time

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1 interval we choose?

2 And maybe we can link them. Maybe let's  
3 ask the lower bound of success and then what time  
4 interval you think it should be checked at.

5 DR. WITTEN: That would be great.

6 MEMBER MABREY: As far as revision surgery  
7 goes at one year, the lower bound of success should be  
8 100 percent.

9 CHAIRPERSON YASZEMSKI: No revisions at  
10 one year?

11 MEMBER MABREY: No revisions or 100  
12 percent success, zero percent failure, no questions  
13 asked.

14 CHAIRPERSON YASZEMSKI: At one year.

15 MEMBER LARNTZ: Infinite sample size.

16 CHAIRPERSON YASZEMSKI: Dr. Finnegan?

17 MEMBER FINNEGAN: Can I do a little  
18 editorializing here?

19 CHAIRPERSON YASZEMSKI: Yes, ma'am.

20 MEMBER FINNEGAN: I think, with all due  
21 respect to Dr. Jacobs, if you go back and look at why  
22 the JBJS and other journals went to two years of data

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1 is because there, in fact, were significant problems  
2 with total joint replacements between one and two  
3 years. I think that is actually the set standard in  
4 our literature for total joints, is 24 months. So I  
5 would say it should be zero revisions at 24 months.

6 CHAIRPERSON YASZEMSKI: Thank you.

7 Dr. Kim?

8 MEMBER KIM: I would agree with that.  
9 When you look at those graphs, it is not a flat line  
10 between one to two years. There is a slight slope.  
11 So it doesn't tip off until ten years, but the further  
12 out you go, the more you can pick up.

13 So two years has been the standard. I see  
14 no compelling reason to change it.

15 CHAIRPERSON YASZEMSKI: Thanks.

16 Dr. Naidu?

17 DR. WITTEN: Excuse me. Does either of  
18 you have a comment on the lower bound of the 95  
19 percent confidence interval?

20 MEMBER KIM: I would also say zero percent  
21 is what I would expect.

22 MEMBER FINNEGAN: And that was my comment,

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1 zero.

2 DR. WITTEN: Oh, I'm sorry. I missed  
3 that.

4 MEMBER NAIDU: I concur.

5 CHAIRPERSON YASZEMSKI: Thank you.

6 Dr. Larntz?

7 MEMBER LARNTZ: This exercise is one that  
8 is so hard to do in non-inferiority studies. Zero is  
9 a wonderful number. We would love to see zero, but we  
10 can't do a study where zero is the upper bound of our  
11 confidence or failure. We have to have some.  
12 Something can go wrong.

13 If we only accept devices that show zero,  
14 the best thing to do if you are the manufacturer --  
15 don't listen, manufacturers -- the best thing is to  
16 not do very many patients.

17 You are more sure to get zero than any  
18 other number. We have got to decide. If one percent  
19 were the true rate, would you be happy? Maybe not.  
20 But you have got to make a decision.

21 This is when I have to go back to  
22 clinicians. I'm sorry I am doing this. But you have

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1 to go back to clinicians and say, "You have got to  
2 give some number that is a reasonable target and then  
3 some number that is greater than that with respect to  
4 failures that tell you it would be" -- I think I said  
5 it. How good does it have to be to be okay?

6 We are not asking for the best possible,  
7 but it has got to be comparable to the ones we see.  
8 Are there revisions in the first year? Yes, there  
9 are. I mean, the data show there are revisions. I'm  
10 sorry. It's not zero. Does every new device that  
11 comes on have to have zero showing? Do very few  
12 patients. You will get zero more often than not.

13 So I submit I appreciate Dr. Witten  
14 jumping in because I was uncomfortable with where we  
15 were going with respect to accepting my comments on  
16 the endpoints. The important thing is the clinical  
17 decision of what the appropriate rate is and then have  
18 a bound that's above that that says it's okay. That  
19 is what we are asking for.

20 I really don't want to do it statistically  
21 because we can always make up deltas, and we do it all  
22 the time. But it's not our job. It's your job. The

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1 clinician will say, "You're the statistician." No,  
2 it's not. It's the clinicians' job to decide what  
3 that margin of inferiority is. How bad can it be so  
4 you're still okay with it?

5 So I apologize for the lecture, but a zero  
6 to me is not an acceptable number.

7 CHAIRPERSON YASZEMSKI: Thanks, Dr.  
8 Larntz.

9 Dr. Besser?

10 MEMBER BESSER: I looked forward to having  
11 absolutely nothing to offer this afternoon as an  
12 engineer and since this was looking at clinical. But  
13 as I read the guidance document, what they are  
14 actually looking for is a 95 percent success rate.

15 How they are defining it as success for  
16 one patient is you are a success if you have no  
17 device-related complications, no revision surgery, and  
18 a Harris Score of at least 80. So that is for an  
19 individual patient. That is a fine criteria because  
20 every individual is either a success or a failure, not  
21 to be too hard on you all.

22 But, in fact, for the device, the rate of

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1 success for the device, they want 95 percent patient  
2 successes.

3 DR. WITTEN: Well, I was following Dr.  
4 Larntz's suggestion looking at each endpoint  
5 individually, but maybe we should go back to what is  
6 in the guidance document and I should say if you look  
7 at this individual patient success definition for the  
8 composite, is what they proposed of 95 percent success  
9 meeting with the non-inferiority margin of 4 percent?

10 So that means that if the observed rate in  
11 the study with this sample size proposed in the  
12 guidance document is 95 percent, then the true rate  
13 for patient success could be as low as 91 percent,  
14 which may be okay, but that is really what I am asking  
15 if we take that target because that is going to  
16 determine what the study looks like.

17 So maybe I should go back and since that  
18 is the way you are looking at it is look at their  
19 definition of individual patient success look at the  
20 composite endpoint. Then the question is, is it  
21 acceptable to have a study that can demonstrate that  
22 the true rate for the device is no less than 91

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1       percent? Is that okay? The true rate of overall  
2       composite success is no worse than 91 percent.

3               So, Dr. Larntz, I hope I said that right.

4               MEMBER LARNTZ: It is the confidence  
5       bound. The true rate would be if it is 95, the true  
6       rate is 95, I think Phyllis pointed out in her sample  
7       size, you actually have to achieve 94 to make sure a  
8       confidence bound was greater than 91, your lower  
9       confidence bound. So, actually, you could never  
10      achieve right at the 91. You have to achieve  
11      something bigger than that, have a lower confidence  
12      bound that is at least 91.

13              DR. WITTEN: So the guidance document is  
14      really proposing 91 as the --

15              MEMBER LARNTZ: As the lower confidence.  
16      The way I think of it is you have got a target of 95  
17      percent, but you want to prove to statistically show  
18      that you are no worse than 91 percent.

19              DR. WITTEN: Right.

20              MEMBER LARNTZ: You statistically show  
21      what you should do with a 95 percent confidence bound.

22              DR. WITTEN: So I guess my question, then,

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1 is, is 91 percent for this composite endpoint good  
2 enough?

3 CHAIRPERSON YASZEMSKI: Let's go back to  
4 Dr. Besser and have you start with asking if that is  
5 okay. If a success per patient is that that patient  
6 has not had a revision, has not had an adverse event,  
7 and has a Harris Hip Score above 80, are you  
8 comfortable with a study, then, that shows that there  
9 are at least 91 percent successes before saying a  
10 device is okay? What do you think?

11 MEMBER BESSER: Now I will put back on my  
12 engineer hat and say I am not sure where medical  
13 science is here. I would love to see it a little  
14 higher, but that's --

15 CHAIRPERSON YASZEMSKI: Okay. That's  
16 okay. Well, I am going to go back to Dr. Doyle and  
17 ask, if you are the person who is about to get it,  
18 would you accept a study like that that said 91  
19 percent of the people in the test group did okay?

20 MEMBER DOYLE: I wouldn't be really happy  
21 with it. And also since most people look at the  
22 Harris Hip Score of 90 or better, I think the

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1 combination of 91 and an 80 score would make me a  
2 little nervous.

3 CHAIRPERSON YASZEMSKI: Okay. Now let's  
4 come back to Dr. Mabrey with these news things. We  
5 all wanted zero percent revisions and zero adverse  
6 events. If we take a composite score, both of those  
7 are in a successful patient. What do you think now  
8 about going back to composite, instead of looking at  
9 things separately?

10 MEMBER MABREY: Well, I think you have to  
11 look at a composite score because everybody wants to  
12 have a great result. We know we are not going to do  
13 that, but I think in terms of the individual  
14 components of that composite, we definitely don't want  
15 the implant to fail at all. And we don't want any  
16 revision surgeries.

17 I think the sponsors have been very  
18 conservative in setting 80. I agree if everyone in a  
19 hip study had a Harris Hip Score of 80 at one year or  
20 at 2 years, I would be a little suspect. What they  
21 are doing is they are setting a lower bound.

22 We have all had patients like this. There

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1 will be those patients who just don't get a whole lot  
2 better or those patients that you took from a Harris  
3 Hip Score of 10, brought them out of their wheelchair,  
4 and now they are sort of shuffling around their  
5 apartment now and they're extremely happy, but they  
6 may only have a hip score of 75 or 80. For them, that  
7 is excellent. That may get to one of your other  
8 points, too. What is the delta in terms of change in  
9 that score is predicting improvement.

10 If we are looking at a 95 percent  
11 confidence interval for the composite score -- and,  
12 again, I appreciate all of the statistics lectures  
13 these past two days, but I can't retain all of them.  
14 But if 91 percent is the lower bound -- and I think  
15 that is the question you are asking -- then that would  
16 represent an actual point of, what, 94 percent?

17 MEMBER LARNTZ: It would have to be 94  
18 with the sample size that Ms. Silverman derived for  
19 that situation, yes.

20 MEMBER MABREY: Ninety-four percent with  
21 a sample size of, what, 270?

22 MEMBER LARNTZ: Two sixty-five, I think it

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1 was.

2 MEMBER MABREY: Two hundred sixty-five  
3 patients?

4 MEMBER LARNTZ: If I remember right,  
5 something like that, yes, 270.

6 MEMBER MABREY: I think at that point,  
7 given what I know about my patient population, I think  
8 I would be happy with that. And then having the  
9 criteria of no failures and no revisions will  
10 certainly bring out those devices that there is a  
11 manufacturing defect, there is a design defect, or  
12 whatever. And then we have the backup with the MDR.  
13 So I am comfortable with 94 or 95 percent.

14 MEMBER LARNTZ: Can I follow up with a  
15 question?

16 CHAIRPERSON YASZEMSKI: Thank you, Dr.  
17 Mabrey.

18 Yes. Go ahead, Dr. Larntz.

19 MEMBER LARNTZ: Would you be satisfied --  
20 I just want to make sure we understand this. Would  
21 you be satisfied if all of those failures, none of the  
22 failures were Harris hip, they were all revisions?

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1 Would you be satisfied with a lower bound of 91  
2 percent on revisions?

3 MEMBER MABREY: No, I would not.

4 MEMBER LARNTZ: But that's what a  
5 composite allows you to have happen. That's why you  
6 have to think. I apologize for going against that,  
7 but you have to think. When you have a composite, you  
8 have to think that somehow the case is the composite  
9 won't be distributed. You have to distribute it in a  
10 way that people might not find acceptable.

11 MEMBER MABREY: Well, then we bring it  
12 around to this point. What we really want is no  
13 failure, no revision. Take that out and take that as  
14 a separate endpoint. All right?

15 Take this out of the composite endpoint  
16 now because if you are really thinking that you really  
17 don't want any revisions or any failures, what you are  
18 really looking at is patient function at the end of  
19 one or two years. That may not be possible. There is  
20 going to be a revision in there somewhere, for  
21 whatever reason.

22 So given that, if we were going to

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1 separate the different components, then I would have  
2 to give you a number of 99 or something for failure  
3 and for revision because there is going to be a  
4 revision in that group of 260 or 70 patients.

5 CHAIRPERSON YASZEMSKI: Thanks, Dr.  
6 Mabrey.

7 Ms. Silverman?

8 MS. SILVERMAN: Yes. I wanted to throw  
9 something out to you. I thought that you might not be  
10 happy with that lower bound of 91 percent. So I kind  
11 of worked the numbers to see what it would take to get  
12 a lower lower bound of 95 percent.

13 Using a comparable sample size of 235, if  
14 you move your target value to 98 percent and you use  
15 a delta of 3 percent, then your lower bound is still  
16 above 95 percent. And the observed success rate that  
17 you would have to get in your study is 97 and a half.

18 So if you see 97 and a half percent in  
19 your study, you can be 95 percent confident that the  
20 lower bound or the minimum guarantee is 95 percent or  
21 higher. So it's kind of like the comparable sample  
22 size, but you just up that target value. And then

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1 your minimum guarantee is more acceptable.

2 CHAIRPERSON YASZEMSKI: Thanks, Ms.  
3 Silverman.

4 May I just before I come over to you, Ms.  
5 Maher, Dr. Doyle, Dr. Mabrey, under those conditions  
6 that Ms. Silverman just stated, what would you say to  
7 Dr. Larntz's question, suppose you had this 98 percent  
8 and all of them were adverse events or revisions?  
9 Would you be okay with that?

10 MEMBER MABREY: Ninety-seven or 98  
11 percent. And they were either an adverse event or --

12 CHAIRPERSON YASZEMSKI: Or a revision.  
13 Would that be an acceptable number? It wasn't okay to  
14 you at 91. Would it be okay at 98?

15 MEMBER MABREY: I think I could sleep at  
16 night.

17 CHAIRPERSON YASZEMSKI: Say again the  
18 number, Ms. Silverman, so we all understand them.

19 MS. SILVERMAN: The target value would be  
20 98 percent. That is better than the 95 percent that  
21 we were talking about. And we would want to be  
22 assured that we are within 3 percent of that, meaning

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1 95 percent or greater.

2 And that could be done with the 235  
3 patients and getting an observed success rate in your  
4 study by the definition of those three criteria, no  
5 revision, no complication, and a Harris Hip Score of  
6 greater than 80. So number of patient successes would  
7 be 97 and a half. And then you could be comfortable  
8 that it was at least 95.

9 CHAIRPERSON YASZEMSKI: So what would be  
10 the answer to Dr. Larntz's question? If all the  
11 failures were adverse events or revisions, how many  
12 would there be in the situation you just --

13 MS. SILVERMAN: If all of the --

14 CHAIRPERSON YASZEMSKI: If all of the  
15 patient failures were either an adverse event or a  
16 revision --

17 MS. SILVERMAN: Then you probably wouldn't  
18 make your 97 and a half percent success rate.

19 CHAIRPERSON YASZEMSKI: No. I'm saying if  
20 you made your success rate but every failure that  
21 occurred wasn't a failure because of Harris Hip Score  
22 but was adverse event or --

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1 MS. SILVERMAN: You couldn't distinguish  
2 that from this.

3 CHAIRPERSON YASZEMSKI: Dr. Stulberg?

4 MEMBER LARNTZ: But if all your failures  
5 -- I think you have something like six failures or  
6 seven failures. I can't remember which it would be in  
7 that case. They would be six or seven revisions in  
8 that case.

9 MEMBER MAHER: Can I make a comment first?  
10 Let's be honest.

11 CHAIRPERSON YASZEMSKI: Go ahead.

12 MEMBER MAHER: We're manufacturers. We  
13 make devices to be sold. If we did a clinical study  
14 and everybody got the right Harris Hip Score and  
15 everything else but we had enough failures to make it  
16 still pass but be at the bare minimum, we are not  
17 going to go forward with that product anyway. I mean,  
18 there has got to be a little bit of common sense in  
19 here.

20 CHAIRPERSON YASZEMSKI: Thank you.

21 MEMBER MAHER: We are using a composite  
22 because it makes sense because we are not going to

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1 have no revisions. We are not going to have perfect  
2 patient compliance because we never do. So let's try  
3 and use some common sense.

4 CHAIRPERSON YASZEMSKI: Dr. Stulberg?

5 DR. STULBERG: I think that was along that  
6 line. In the practical matter of sorting how things  
7 go wrong, if you have 5 failures that are due that out  
8 of this 100 patients or 200 or whatever, 5 percent,  
9 and all of them are related to revision, then there  
10 are things of technique, implant sizing, device.  
11 There are a bunch of issues involved in that failure.

12 So if you are one of those few groups that  
13 are studying that patient, you are not going to be  
14 very happy and allow that device to go forward. In  
15 allowing a clinical part of this to be in here, that  
16 Harris Hip Score, you have to build in some reasonable  
17 range where you are going to lose patients, you are  
18 going to have patients who start lower with the Harris  
19 Hip Score and still improve but are in the lower 80s.  
20 You have to build some feature. And that's fair.

21 I think that was the measure behind trying  
22 to put it composite, is that ultimately with the

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1 patient walking out the door and walking home, it's a  
2 composite picture of us doing our job right, the  
3 device doing what it is supposed to do and the patient  
4 participating. We needed to come up with something  
5 that was fair.

6 CHAIRPERSON YASZEMSKI: Thanks so much,  
7 Dr. Stulberg.

8 Dr. Doyle?

9 MEMBER DOYLE: I guess I had statistics  
10 too long ago because I am confused. We are talking  
11 about the composite. And, yet, it seems to me what we  
12 are talking about now is the variation among each of  
13 the three parts of the composite.

14 I thought that it didn't matter which one  
15 of them that failed. What we were looking at and what  
16 we needed the confidence intervals for would be the  
17 patient. But Dr. Besser was saying that it is either  
18 a yes or it is a no.

19 Yet, it seems to me that, instead of  
20 taking the thing as a whole, we are dissecting out  
21 parts. And it really doesn't matter because if it's  
22 yes, it's yes. And if it's no, it's no. And it's the

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1 aggregate patient success that I thought we were  
2 looking at, not the individuals. And it would seem to  
3 me that by doing it with the aggregate or the  
4 composite, that you have a better chance of picking up  
5 something because each of those would contribute to a  
6 yes or a no patient.

7 CHAIRPERSON YASZEMSKI: Thanks.

8 Dr. Larntz?

9 MEMBER LARNTZ: And the difficulty I have  
10 with the composite is the components of the composite  
11 are not equal. If someone has a revision, that's much  
12 worse than someone who has a 79 Harris Hip Score.

13 So in my estimation, we should have -- and  
14 that is what I said to my comment -- a standard for  
15 revision. We should also have a standard for Harris  
16 Hip Score. That's fine.

17 Actually, I don't know, but I thought 95  
18 percent success rate on the Harris hip would be just  
19 fine for above 80. But revisions, I would think that  
20 a one percent target with an upper bound of either  
21 three or four percent would have been just fine. You  
22 know, that is what I would look for.

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1                   And if you look in the ablation catheter,  
2                   they have a two and a half percent major complication  
3                   rate with an upper bound of seven. That is actually  
4                   pretty liberal statistically. But I think that we  
5                   have to be very clear.

6                   I heard what Ms. Maher said, which was  
7                   that, oh, if we have all of those, we aren't going to  
8                   do it. Use common sense. Well, we have to be careful  
9                   using common sense. Well, why don't we just make a  
10                  standard for revision? And we can get that.

11                  It may not be fair, and I am never fair.  
12                  But that's okay because I am a statistician. But what  
13                  I want to say is maybe we really need to go look at  
14                  the data to get more informed about these. We don't  
15                  have a meta analysis of these components.

16                  Clearly the data are there. Clearly  
17                  they're there. I mean, if these registries are at all  
18                  complete, we have got so much data. I think we have  
19                  a lot of data.

20                  We should be able to inform ourselves  
21                  without guessing about what the value should be. And  
22                  then we would know what the characteristics are of the

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1 current approved hips replacement systems. And we  
2 could use those values to inform us.

3 I think it may be unfair. It was unfair  
4 of me to ask you to give real numbers because I think  
5 that we aren't fully informed, but the data are there.

6 CHAIRPERSON YASZEMSKI: Thanks, Dr.  
7 Larntz.

8 Dr. Doyle, did you have another comment?

9 MEMBER DOYLE: No.

10 CHAIRPERSON YASZEMSKI: Ms. Maher?

11 MEMBER MAHER: Not right now.

12 CHAIRPERSON YASZEMSKI: Other comments?

13 (No response.)

14 CHAIRPERSON YASZEMSKI: Dr. Witten, as you  
15 can see, there is lots of disagreement on this issue.  
16 We have had a fairly thorough discussion, but the  
17 issues that remain are whether to consider the  
18 composite score as best or maybe have several scores,  
19 one of which might be a composite; for example,  
20 revisions and adverse events together as a composite,  
21 and have a certain confidence interval and target and  
22 another; i.e., the Harris Hip Score as a separate.

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1           It appears that it is going to take more  
2       discussion and more work between the clinicians and  
3       OSMA and the FDA. I want to be certain that I ask  
4       that you feel you have had enough discussion at this  
5       point.

6           DR. WITTEN: Yes. Thank you.

7           CHAIRPERSON YASZEMSKI: Thank you.

8           We will move on to number two, study  
9       duration. We have read it before. We will just ask  
10      everybody to look at it again and start talking. The  
11      issue, of course, centers around whether one year or  
12      two years would be appropriate.

13           You heard from our clinicians, Dr.  
14      Stulberg and Dr. Jacobs, that the difficulties with  
15      total hip replacements were becoming evidenced at 10,  
16      15, and perhaps 20 years and that although the line  
17      between one and two years is not flat, as Dr. Kim  
18      mentioned, it's also not very steep and whether  
19      problems can be identified adequately short-term  
20      problems in a year or whether we need two years.  
21      Let's maybe start. Dr. Naidu, can we ask your  
22      comments on this issue?

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1 MEMBER NAIDU: Yes. I am not sure as to  
2 why we should be changing from two years to one year.  
3 I mean, it appears as if there are other problems that  
4 surfaced between one and two years. I don't see the  
5 benefit of shortening this follow-up.

6 CHAIRPERSON YASZEMSKI: Okay. Thank you.

7 Dr. Larntz?

8 MEMBER LARNTZ: I think if we choose our  
9 endpoint appropriately and if we analyze, could get  
10 the data from historical controls, I see no problem  
11 using one year if we can get that data. If all we are  
12 using is published literature, that is at two years.  
13 And I think we would have problems.

14 CHAIRPERSON YASZEMSKI: Okay. Thanks, Dr.  
15 Larntz.

16 Dr. Besser?

17 MEMBER BESSER: Nothing to add.

18 CHAIRPERSON YASZEMSKI: Ms. Maher?

19 MEMBER MAHER: I actually don't really see  
20 a problem with sticking with the one year, again  
21 depending on getting all of the right data points.

22 CHAIRPERSON YASZEMSKI: Thank you.

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1 Dr. Doyle?

2 MEMBER DOYLE: I favor two-year.

3 CHAIRPERSON YASZEMSKI: Dr. Mabrey?

4 MEMBER MABREY: Again, it has been pointed  
5 out we live in a very mobile society. I think if we  
6 extend it to two years, it is possible that you may  
7 actually be losing some data because of that. As a  
8 clinician, I can tell you that my revision rate and  
9 device failure rate between one and two years is  
10 almost nonexistent.

11 As Dr. Jacobs and Dr. Stulberg have  
12 pointed out, the biggest problems with these implants  
13 is going to occur many, many years out, so far out  
14 that it is not feasible to have a study like that. I  
15 would add that even those problems eventually should  
16 be picked up by the National Hip Registry once we get  
17 that up and going.

18 So I would support a one-year limit with  
19 the understanding that many of these studies are  
20 ongoing, that these surgeons still want to publish in  
21 Dr. Heckman's magazine, and if they don't provide  
22 two-year data, it ain't going to go in.

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1                   So I think the data will be there anyway,  
2                   but I think that shortening the time frame from two  
3                   years to one year does encourage a little bit more in  
4                   the way of innovation. And I do not see an adverse  
5                   impact on patient safety.

6                   CHAIRPERSON YASZEMSKI: Thank you, Dr.  
7                   Mabrey.

8                   Dr. Finnegan?

9                   MEMBER FINNEGAN: I think if we are going  
10                  to use historical controls for our control group and  
11                  they are two years, then we should stay with two  
12                  years.

13                  CHAIRPERSON YASZEMSKI: Thank you.

14                  Dr. Kim?

15                  MEMBER KIM: I said two years in the  
16                  context of keeping the composite score, but if we are  
17                  going to separate out each score; for example, for the  
18                  rate of revision, then I see no utility in waiting two  
19                  years if we have one-year data. So if we know that at  
20                  one year, the revision rate should be one percent and  
21                  at two years, it should be two percent, then we could  
22                  just easily choose the one-year mark and put the

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1 requirement that there is only a one percent revision  
2 rate.

3 So if we separate it out and we have the  
4 data like Dr. Larntz already described, then I would  
5 see no problem going to one year, but we would have to  
6 have that one year data available.

7 CHAIRPERSON YASZEMSKI: Thanks, Dr. Kim.

8 Dr. Witten, again there is some  
9 disagreement among the panel members. Dr. Larntz has  
10 indicated that due to the long history of total hip  
11 arthroplasty in the United States and in the world,  
12 good data exists if it can be gotten. It might take  
13 a little work to do, but it exists.

14 In this instance, historical controls may  
15 be okay. We have heard from our clinicians that some  
16 would be comfortable with one-year data, but some  
17 would want two-year data. I think that it would be  
18 really impossible for us to give you a consensus  
19 statement, but to say that these need to be looked at  
20 probably on a case by case basis and that there would  
21 be some support in certain instances for going to  
22 one-year data.

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1 Have we discussed this enough?

2 DR. WITTEN: Yes. Thank you.

3 CHAIRPERSON YASZEMSKI: You're welcome.

4 Number three, this is the question  
5 regarding patient selection. We have read it before.  
6 Please, everybody, take a second and look at it.  
7 Inclusion and exclusion criteria. We start this time,  
8 Dr. Finnegan, with you. What do you think about  
9 patient selection for studies?

10 MEMBER FINNEGAN: Well, I guess I will  
11 start it with the easy stuff, which is obviously those  
12 patients who are considered not appropriate for  
13 clinical trials per FDA. And that is pregnant and  
14 prisoners and those with psychological problems  
15 obviously need to be excluded.

16 The known factors affecting total joints  
17 include BMI or weight and activity levels and  
18 obviously diagnoses. So I would say that those  
19 standard internationally accepted exclusions should  
20 obviously be excluded and that there needs to be some  
21 consideration for inclusion/exclusion related to the  
22 known biomechanical problems of the implants as well

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1 as the disease process being treated. That is not  
2 very detailed.

3 CHAIRPERSON YASZEMSKI: Thank you. Thank  
4 you.

5 Dr. Kim?

6 MEMBER KIM: I would agree with Dr.  
7 Finnegan that if you are going to be in a study, there  
8 should be some basic exclusions, like psychiatric  
9 illness, pregnancy, et cetera.

10 I would want a study population that  
11 mimics the general population that would be receiving  
12 these implants. So I wouldn't want to have a study  
13 that cherry-picked all the skinny, healthy people  
14 because when it does come out to market, a lot of  
15 non-skinny people are going to get it, too.

16 So my feeling is to limit patient  
17 selection and try to keep it as representative and to  
18 the general population as possible.

19 CHAIRPERSON YASZEMSKI: Thanks, Dr. Kim.

20 Dr. Naidu?

21 MEMBER NAIDU: Yes. I would echo the  
22 sentiments of Dr. Kim. In addition, as far as the

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1 specific Harris Hip Score requirements, you know, I  
2 would defer that to the total joint colleagues.

3 CHAIRPERSON YASZEMSKI: Thank you.

4 Dr. Larntz?

5 MEMBER LARNTZ: Yes. I would just mimic  
6 the fact that we want this to match the population  
7 that is going to receive it in the long run. I think  
8 that this may not be the population for which we have  
9 a historical data. So there may be some work with  
10 respect to matching a population that is different  
11 from the one in which we have our standards set.

12 CHAIRPERSON YASZEMSKI: Thanks, Dr.  
13 Larntz.

14 Dr. Besser?

15 MEMBER BESSER: Nothing else to add.

16 CHAIRPERSON YASZEMSKI: Thank you.

17 Ms. Maher?

18 MEMBER MAHER: Yes. I would actually like  
19 to ask Mr. Batts to comment on how they came up with  
20 the patient selections they have in there.

21 CHAIRPERSON YASZEMSKI: Thank you.

22 Mr. Batts?

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1 MR. BATTS: Yes. One thing I wanted to  
2 say was that this does not replace some of the common  
3 deliberations that a sponsor goes through with FDA.  
4 There will still remain -- even though this document  
5 will standardize or put benchmarks for some things, it  
6 does not remove the negotiations that would go on  
7 between FDA and a sponsor insofar as  
8 inclusion/exclusion criteria, radiographic type  
9 analysis. Those things are all still going to have to  
10 be worked out on a device base.

11 CHAIRPERSON YASZEMSKI: Thank you.

12 Dr. Doyle?

13 MEMBER DOYLE: I would agree and second  
14 what Dr. Larntz said. I would like to know it was  
15 tried on somebody like me, not somebody like Twiggy.

16 CHAIRPERSON YASZEMSKI: Thank you, Dr.  
17 Doyle.

18 Dr. Mabrey?

19 MEMBER MABREY: I will just echo the  
20 panel's comments that it should be a representative  
21 population, generally represented for that population  
22 that the surgeon is dealing with. But I would also

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1 add that we need to record, we ought to record those  
2 demographic characteristics, age, sex, race, and  
3 weight, which is actually part of the Harris Hip Score  
4 if you fill the whole thing out and do all of the  
5 calculations. So we need to capture at least that  
6 demographic data.

7 CHAIRPERSON YASZEMSKI: Thanks, Dr.  
8 Mabrey.

9 Dr. Witten, there is a general consensus  
10 on this question that we ought to include standard  
11 clinical study inclusion/exclusion criteria for hips,  
12 including the body mass index, absence of such  
13 conditions as psychiatric conditions; pregnancy; and  
14 diagnosis; and, most importantly, that the study  
15 population ought to mimic the population who is going  
16 to get this implant.

17 Have you additional questions or have we  
18 discussed this appropriately?

19 DR. WITTEN: Thank you.

20 CHAIRPERSON YASZEMSKI: You're welcome.

21 Question four, outcome measures. Again  
22 let's all please read it. Look at for a second. And

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1 we will start this time with Dr. Besser.

2 I will note for the record, Dr. Besser, as  
3 you are preparing to speak, that you can include the  
4 discussion we had in question one because we discussed  
5 outcomes and how to either group them or separate them  
6 quite thoroughly. But if you see additional outcome  
7 measures that should be discussed, please bring them  
8 up now.

9 MEMBER BESSER: I had a question either  
10 for the sponsor or for Ms. Maher. What does it cost  
11 to add something like the SF-36 or the WOMAC paper and  
12 pencil test to a study such as this?

13 CHAIRPERSON YASZEMSKI: Mr. Batts?

14 MR. BATTS: Yes. The SF-36 I couldn't  
15 give you an exact dollar figure, but there is a  
16 licensing fee on the SF-36. The WOMAC, there has been  
17 some discussion on that. I think in our last meeting  
18 that had we OSMA, they are going to start charging a  
19 licensing fee for that.

20 There are other subjective questionnaires  
21 in the literature. There is the musculoskeletal  
22 functional assessment that Swiontkowski did at

1 Minnesota. There are a few others that can be done.  
2 But I would say that the vast majority, WOMAC, SF-36,  
3 are going to require licensing fees. Let's say for a  
4 200-patient study, you will pay probably 5 to 10  
5 thousand dollars for that to be done.

6 MEMBER MABREY: Mr. Chairman?

7 CHAIRPERSON YASZEMSKI: Yes, sir? Dr.  
8 Mabrey?

9 MEMBER MABREY: As a point of information,  
10 having looked at the online version of the SF-36,  
11 version 2 last night, the license fee is \$199  
12 non-refundable. And then every score entered after  
13 that is 50 cents each. That is for each individual  
14 study.

15 Having said that, I would also point out  
16 that there are additional costs involved in  
17 administering the questionnaire, which includes the  
18 personnel necessary to enter that data or to collect  
19 the data first; second, to actually enter that data  
20 into the computer.

21 And then, as Dr. Jacobs has pointed out,  
22 there is a strain on the clinician's office. He needs

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1 to keep the people moving through the office and  
2 spending time, taking time to do those questionnaires  
3 properly can really slow one's office down.

4 I am not saying that we should not collect  
5 the data. I am just pointing out that there are  
6 additional hidden costs to administering those  
7 studies.

8 CHAIRPERSON YASZEMSKI: Okay. Thank you,  
9 Dr. Mabrey.

10 MEMBER BESSER: Yes. And I guess my  
11 question was more if you include all of those costs,  
12 understanding that at some point, you make a study  
13 unwieldy and surgeons are going to decide, "I don't  
14 have time for all the rest of this. I'm just going to  
15 do" --

16 MR. BATTS: And that happens quite a bit  
17 when it gets weighed down by those kinds of issues.

18 MEMBER MABREY: It adds about two minutes  
19 to the exam. That cost is excessive to most  
20 clinicians.

21 CHAIRPERSON YASZEMSKI: Thank you. Dr.  
22 Besser, have you had an answer?

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1                   MEMBER BESSER: I would love to see some  
2 kind of or would recommend to the FDA that they  
3 include some kind of global patient-centered measure,  
4 such as the SF-36 or the WOMAC. If I get to pick, I  
5 would pick the WOMAC.

6                   CHAIRPERSON YASZEMSKI: Thanks, Dr.  
7 Besser.

8                   Ms. Maher?

9                   MEMBER MAHER: I would actually follow on  
10 to what Dr. Besser said, suggest that the FDA and the  
11 sponsor work together on the studies. And where  
12 something like that seems appropriate for the studies,  
13 they could include it, but it wouldn't be part of the  
14 guidance document, just that we have the guidance  
15 document has the minimum type requirements and then  
16 the negotiations as you are developing your protocol  
17 and your clinical study, that you determine what else  
18 you need besides the minimum requirements.

19                   CHAIRPERSON YASZEMSKI: Thank you, Ms.  
20 Maher.

21                   Dr. Doyle?

22                   MEMBER DOYLE: I have nothing to add to

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1 what Dr. Besser said.

2 CHAIRPERSON YASZEMSKI: Thank you, Dr.  
3 Doyle.

4 Dr. Mabrey, any additional comments?

5 MEMBER MABREY: Yes. I would like to  
6 point out that there are studies available that  
7 correlate to Harris Hip Score quite well with the  
8 SF-36, at least in the physical component, not in the  
9 mental component. So that data is available and it  
10 does give you a reasonable indication of how things  
11 are going.

12 I would say I think that data is important  
13 to collect, but then we have to look at, what are we  
14 evaluating? If we are evaluating the device itself,  
15 it is my impression, my feeling that the Harris Hip  
16 Score does a very good job of evaluating the device.  
17 If we are looking at the SF-36 and the WOMAC -- and  
18 these are very important studies -- now we are looking  
19 at the total hip as a system and as a part of the  
20 community.

21 Now, that may become necessary further on.  
22 And I know that we are not always supposed to look too

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1 far into the future, but some of these total hip  
2 systems involve more than just simple instrumentation.  
3 They involve ways of doing things that involve the  
4 patient in more than just the surgery: preoperative  
5 planning, postoperative anesthesia, that sort of  
6 thing.

7 And some of those protocols may be  
8 pactable and may come before the FDA. That is a  
9 separate issue. No one discounts that that data is  
10 not important. I am not sure that it contributes a  
11 whole lot to the evaluation of a device.

12 CHAIRPERSON YASZEMSKI: Thanks, Dr.  
13 Mabrey.

14 Dr. Finnegan?

15 MEMBER FINNEGAN: Yes. I think at the  
16 minimum, there needs to be and my understanding is  
17 that Mr. Batts said that radiographic follow-up was  
18 already automatically part of the follow-up that they  
19 are recommending, although I didn't see that in the  
20 guidance document. Sir?

21 CHAIRPERSON YASZEMSKI: Is that a question  
22 for him?

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1 MEMBER FINNEGAN: I guess.

2 CHAIRPERSON YASZEMSKI: Mr. Batts?

3 MEMBER FINNEGAN: Did I hear you  
4 correctly?

5 MR. BATTS: It is not part of the  
6 composite criteria. What it does is it is in the  
7 protocol or in the guidance document enough that if an  
8 individual device -- and, again, this doesn't remove  
9 the device by device evaluation into what will go into  
10 a particular protocol, but radiographic analysis will  
11 be something that the FDA and the sponsor look at and  
12 say, "Okay. For this device, these are the migration  
13 values we want to see with these techniques."

14 If we were to put a standardized  
15 radiographic protocol into this document, it would  
16 severely limit its use to a wide range of prostheses.  
17 So it's not a component of the criteria, the success  
18 criteria, but it is in the document insofar as it  
19 recognizes those things may need to be measured  
20 depending on the device.

21 MEMBER FINNEGAN: Okay. You're going to  
22 know before the device what your migration problems

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1 are?

2 MR. BATTS: No. Writing protocol for the  
3 device, as the FDA and the sponsor go back and forth,  
4 we will say, "These characteristics, the  
5 characteristics of this device warrant this type of  
6 radiographic analysis."

7 MEMBER FINNEGAN: Okay. Thank you.

8 I guess I would like to see as an endpoint  
9 some radiographic follow-up. And I also agree with  
10 Dr. Besser that the SF-36 would be or the WOMAC would  
11 be the most idea but certainly some evaluation tool as  
12 well as some concept of the patients' return to their  
13 previous level of activity, whether that is work or  
14 whatever their level of activity was.

15 CHAIRPERSON YASZEMSKI: Thank you, Dr.  
16 Finnegan.

17 Dr. Kim?

18 MEMBER KIM: I have nothing further to  
19 add.

20 CHAIRPERSON YASZEMSKI: Thank you, Dr.  
21 Kim.

22 Dr. Naidu?

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1 MEMBER NAIDU: I have nothing further to  
2 add.

3 CHAIRPERSON YASZEMSKI: Thank you.

4 Dr. Larntz?

5 MEMBER LARNTZ: I am not afraid to add  
6 different endpoints. I just want to make sure that if  
7 we do that, we have a way of evaluating them and  
8 making sure that there is enough of a historical  
9 database to use them. If we are doing this kind of  
10 study, we would have to have that to set up criteria.

11 It is possible to set up criteria that are  
12 different for different devices. So if, for instance,  
13 a radiologic follow-up is worthwhile for some but not  
14 for others, you could have a criteria for doing that.

15 For instance, in the heart valve, there  
16 are different criteria for tissue valves and  
17 mechanical valves with respect to the numbers that the  
18 objective performance criteria have to meet.

19 CHAIRPERSON YASZEMSKI: Thanks, Dr.  
20 Larntz.

21 Dr. Witten, the panel in general has  
22 agreement on additional endpoints added to those that

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1 we discussed in number one. On a case by case basis,  
2 it would be good to have some sort of radiologic  
3 evaluation. That could be discussed between the  
4 petitioner and the FDA as to which type exactly and  
5 some sort of outcome analysis, be that outcome  
6 analysis in SF-36, a WOMAC, or some return to  
7 activity, which may be included in those other  
8 clinical outcomes analyses as a part of them and may  
9 or may not need to be done separately.

10 Have you additional questions on this  
11 question or have we discussed it appropriately?

12 DR. WITTEN: Thank you.

13 CHAIRPERSON YASZEMSKI: Let's move on to  
14 number five, post-market studies. Again, look at it,  
15 please. This time, Dr. Kim, when you have an idea, we  
16 will start with you.

17 MEMBER KIM: Give me a moment.

18 (Pause.)

19 MEMBER KIM: Well, given the fact that we  
20 are not going to see failure rates for 5 to 10 to 15  
21 years, I think post-market studies are appropriate.

22 CHAIRPERSON YASZEMSKI: May I ask, Dr.

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1 Kim, would you think it would be appropriate upon the  
2 manufacturer to do the study or the clinical community  
3 who are going to do studies and follow their patients  
4 through societies like the hip society?

5 MEMBER KIM: I think it would be  
6 unreasonable to expect industry to follow patients for  
7 10, 15, 20 years. I think it is incumbent on  
8 practitioners in academic centers to have that role.

9 CHAIRPERSON YASZEMSKI: Thank you.

10 Dr. Naidu?

11 MEMBER NAIDU: Yes. I think post-market  
12 studies would be valuable. Especially specific  
13 questions would be the number of revisions and X-ray  
14 follow-up, as Dr. Finnegan suggested, would be useful.

15 CHAIRPERSON YASZEMSKI: Thank you.

16 Dr. Larntz?

17 MEMBER LARNTZ: It is difficult for me to  
18 think of exactly the nature of a post-market study for  
19 this that won't go long enough to be worthwhile. So  
20 I will just stop at that.

21 CHAIRPERSON YASZEMSKI: Thank you.

22 Dr. Besser?

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1 MEMBER BESSER: Nothing to add.

2 CHAIRPERSON YASZEMSKI: Ms. Maher?

3 MEMBER MAHER: Nothing to add to what Dr.  
4 Larntz said.

5 CHAIRPERSON YASZEMSKI: Thank you.

6 Dr. Doyle?

7 MEMBER DOYLE: Nothing to add.

8 CHAIRPERSON YASZEMSKI: Thank you.

9 Dr. Mabrey?

10 MEMBER MABREY: I would add that I think  
11 the post-market studies will be out there anyway as  
12 the clinicians continue to follow their patients and  
13 report on them in the orthopedic literature.

14 I guess as a corollary or as an add-on, I  
15 would just make it a responsibility of the  
16 manufacturers to keep the FDA posted as to the  
17 clinical output or the clinical papers generated  
18 related to that device. I don't think that is  
19 overburdensome to keep them updated.

20 CHAIRPERSON YASZEMSKI: Thank you.

21 Dr. Finnegan?

22 MEMBER FINNEGAN: I am going to separate

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1 the question. I think if we decide or if it is  
2 decided that 12 months or one year is good enough  
3 follow-up pre-approval, then I do believe that  
4 post-market studies need to be done probably out to 3  
5 years. If it is decided to go to 24 months, then I am  
6 less certain about post-market studies.

7 CHAIRPERSON YASZEMSKI: Okay. Thank you.

8 Dr. Witten, there is general agreement on  
9 post-market studies that they may occasionally be  
10 appropriate. As Dr. Larntz said, no post-market study  
11 except long-time follow-up of patients by clinicians  
12 is going to answer the 10 to 15 to 20-year question  
13 and maybe even they won't except that problems will  
14 become recognized.

15 There may be some need for X-ray follow-up  
16 specifically if the one-year endpoint is adopted and  
17 also for the follow-up on adverse events and revisions  
18 if the one-year is adopted.

19 Have we discussed this to FDA's  
20 satisfaction?

21 DR. WITTEN: Yes. Thank you.

22 CHAIRPERSON YASZEMSKI: Let's move on to

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1 number six. When we look it over, Dr. Mabrey, I will  
2 ask you to start at number six. Take a second to look  
3 at it and read it.

4 MEMBER MABREY: I think that for the  
5 limited data collection for this GDS, that these hip  
6 systems should be limited to primary total  
7 arthroplasty, either cemented or uncemented, that it  
8 should specifically exclude constrained devices as  
9 these are prone to failure anyway. And it should also  
10 exclude custom devices or one-off devices, such as  
11 custom acetabular cups or prostheses that are designed  
12 for revision.

13 I think if we are only going to look at  
14 things at one year, probably primary joint replacement  
15 is most appropriate and gives us the most consistent  
16 data. Once we get into custom devices, I think it is  
17 a lot harder. Even though it's good to follow that,  
18 I think it is harder to reach a conclusion when your  
19 implants aren't quite the same.

20 Thanks.

21 MEMBER MAHER: Actually, if I can follow  
22 up on that, custom devices would be very difficult to

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1 do a study on anyway because by their definition, they  
2 are made to the doctor's specification for a specific  
3 patient. So it is not really -- that would be up to  
4 a doctor to follow his patients if he was interested.

5 MEMBER MABREY: I am just thinking in  
6 terms of some of the custom cups that are available  
7 that are not quite off the shelf but, like the  
8 orthogenesis --

9 CHAIRPERSON YASZEMSKI: I think we are  
10 probably saying the same thing, but Ms. Maher reminded  
11 us of the definition of custom on a per-patient  
12 prescription. I think that was different than what  
13 Dr. Mabrey was talking about.

14 Dr. Finnegan?

15 MEMBER FINNEGAN: The only thing I would  
16 add is also those devices used in tumors.

17 CHAIRPERSON YASZEMSKI: Tumor devices.

18 Dr. Kim?

19 MEMBER KIM: I think at least for me, the  
20 utility of a guidance document like this is to quickly  
21 assess different types of hip systems. So I don't see  
22 any benefit in limiting the ones that have been looked

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1 at. I would much rather have this guidance document  
2 to help us look at a wide variety of hip systems. So  
3 I don't support limiting the systems.

4 CHAIRPERSON YASZEMSKI: Go ahead, Dr.  
5 Mabrey.

6 MEMBER MABREY: I agree it is important to  
7 look at all systems. And I guess my main point about  
8 looking at primaries is that you would be able to  
9 generate enough numbers to actually make a meaningful  
10 conclusion.

11 If you are looking at some of these tumor  
12 devices and/or prostheses, that sort of thing, it will  
13 certainly take more than a year anyway to generate the  
14 numbers necessary for a good clinical study. And that  
15 is why I brought that up.

16 CHAIRPERSON YASZEMSKI: Thanks, Dr.  
17 Mabrey.

18 Dr. Naidu? Mr. Melkerson?

19 MR. MELKERSON: Just one clarification  
20 point. When you are talking hip systems, in FDA's  
21 definitions, there are semi-constrained total hips and  
22 there are also hip resurfacing total hip replacements.

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1 When you are saying "all hip systems," does it mean  
2 just that, all hip systems?

3 CHAIRPERSON YASZEMSKI: Thanks for  
4 clarification, Mr. Melkerson.

5 Dr. Naidu, either general comments or  
6 response to Mr. Melkerson's clarification?

7 MEMBER NAIDU: Yes. I mean, I think this  
8 should include all hip systems. I'm not sure about  
9 the revision cases.

10 CHAIRPERSON YASZEMSKI: Thank you.

11 Dr. Larntz?

12 MEMBER LARNTZ: Nothing to add.

13 CHAIRPERSON YASZEMSKI: Thank you.

14 Dr. Besser?

15 MEMBER BESSER: Nothing to add.

16 CHAIRPERSON YASZEMSKI: Ms. Maher?

17 MEMBER MAHER: I will go back to the  
18 comment that I made earlier. Since this is a minimum  
19 set of requirements, I think it should include  
20 everything. And when you also include the revisions,  
21 it may be that revisions wouldn't work because you  
22 would need too high a patient population to meet the

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1 demands of what we put in here.

2 But, again, that would be up to  
3 negotiations between the sponsor and the FDA.

4 CHAIRPERSON YASZEMSKI: Thanks, Ms. Maher.  
5 Dr. Doyle?

6 MEMBER DOYLE: Nothing to add.

7 CHAIRPERSON YASZEMSKI: Thank you.

8 Dr. Witten, I am going to submit to you  
9 that we actually do have agreement here, as Ms. Maher  
10 suggested. These are a minimum set of requirements.  
11 And although they should apply to all systems, some of  
12 the less used systems; i.e., the resurfacing systems  
13 that Mr. Melkerson mentioned, the tumor systems,  
14 custom devices, and certain constrained devices and  
15 revision devices would need further negotiation  
16 between FDA. But we do feel that that is a baseline  
17 minimum set of requirements or guidance for  
18 requirements that this should apply to all hip  
19 systems.

20 Have we discussed it adequately?

21 DR. WITTEN: Yes. Thank you.

22 CHAIRPERSON YASZEMSKI: I would like to

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1 ask now. I would like to ask if Dr. Stulberg or Dr.  
2 Jacobs has any closing comments, I would like to  
3 invite them to give. And if they don't, that's okay,  
4 too. Either?

5 DR. STULBERG: I think we want to thank  
6 the panel for their consideration of this document and  
7 the helpful comments they have given.

8 CHAIRPERSON YASZEMSKI: Thanks so much.

9 Dr. Witten, any comments from FDA?

10 DR. WITTEN: I would like to thank OSMA  
11 and AOS members who participated for submitting the  
12 guidance and the panel for discussing it and the FDA  
13 review staff for preparing for this meeting.

14 CHAIRPERSON YASZEMSKI: Thanks so much.

15 I would like also to once again thank the  
16 panel members for their service and their preparation  
17 and participation during the meeting. And we adjourn  
18 this meeting now.

19 MEMBER MABREY: Mr. Chairman, I think we  
20 also should recognize what a great job you have done  
21 over the last two days. You are actually two minutes  
22 ahead of your own schedule.

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1                   This being my first panel, I just want to  
2                   say this has been a very enlightening experience and  
3                   one of the best panels I have ever had an opportunity  
4                   to sit on.

5                   CHAIRPERSON YASZEMSKI: Thank you.

6                   (Applause.)

7                   (Whereupon, at 3:56 p.m., the foregoing  
8                   matter was adjourned.)

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CERTIFICATE

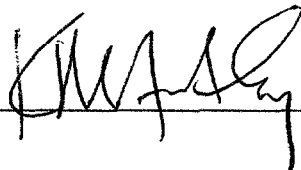
This is to certify that the foregoing transcript in the  
matter of:                   Orthopedic and Rehabilitation  
                                  Devices Panel

Before:                   DHHS/PHS/FDA/CDRH

Date:                   June 3, 2004

Place:                   Gaithersburg, MD

represents the full and complete proceedings of the  
aforementioned matter, as reported and reduced to  
typewriting.

  
A handwritten signature in dark ink, appearing to be "M. J. [unclear]", is written over a horizontal line.